

# RoB 2 Domain 2: Bias due to deviations from the intended interventions

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Trusted evidence.  
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- Deviations from intended intervention and the role of blinding
- Effects of interest
- *Questions*
- Risk of bias in the effect of assignment to intervention
- *Discussion*
- Risk of bias in the effect of adhering to intervention
- *Questions*



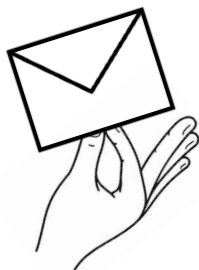
# Risk of bias in randomized trials

*Bias arising from the randomization process*

*Bias due to deviations from intended intervention*

*Bias due to missing outcome data*

*Bias in measurement of the outcome*



Experimental

Comparator

Outcome

Outcome



1.02	3.87
2.20	4.32
1.38	<b>5.44</b>



*Bias in selection of the reported result*

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# Deviations from intended intervention and the role of blinding

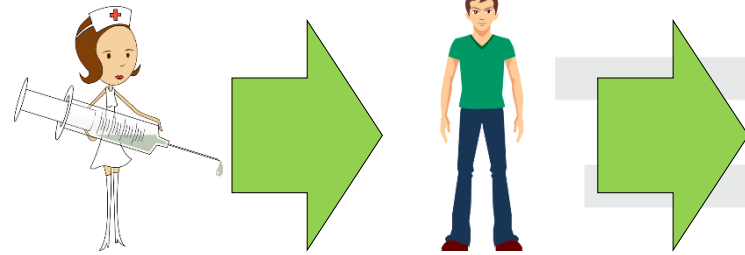


# What are deviations from intended intervention?

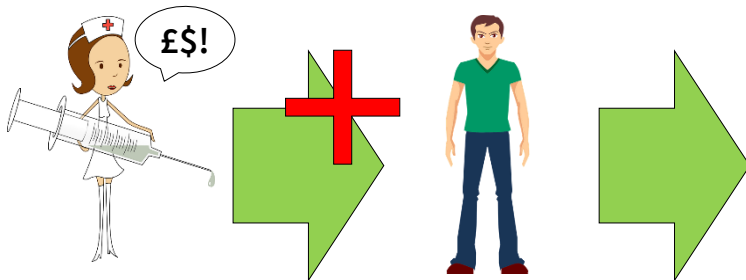
Intended intervention protocol:

Intervention  
provider

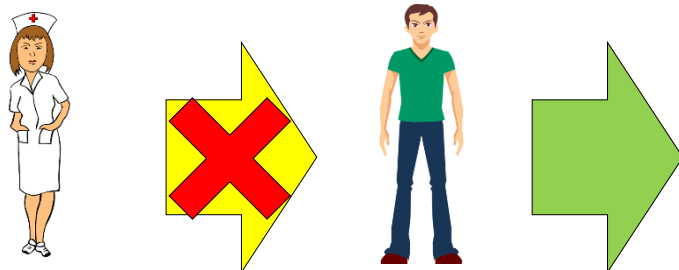
Participant



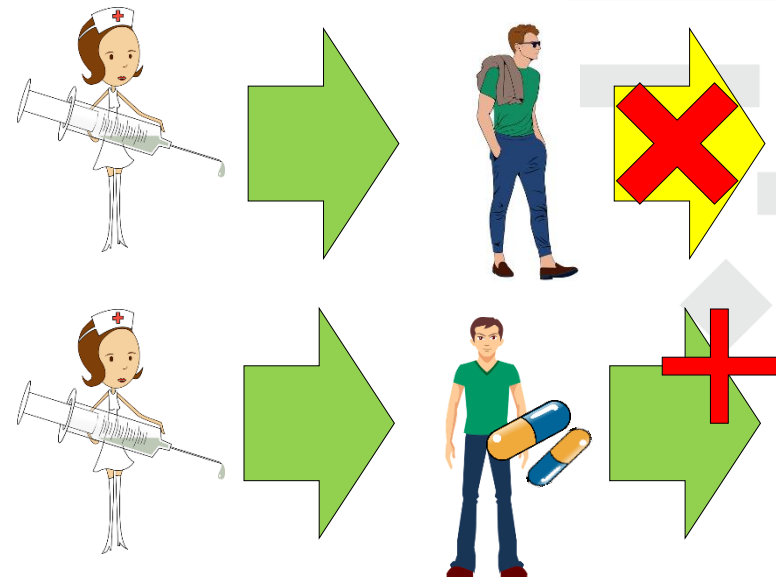
## 1. Additional interventions given



## 2. Failure to implement as intended



## 3. Non-adherence by trial participants



# Deviations from intended intervention (in words)

1. administration by trial staff of **additional interventions** that are inconsistent with the trial protocol (*non-protocol interventions*)
  - non-protocol interventions that affect the outcome of interest can lead to bias in estimated intervention effects
  - if possible, specify potential non-protocol interventions in the review protocol
2. **failure** by trial staff **to implement** the protocol interventions **as intended**
3. **non-adherence** to assigned intervention **by trial participants**

**NB Trial protocols may not fully specify the interventions that are intended**

# Changes to intervention

- It is often intended that the intervention will change over time
- For example, trial investigators may intend that:
  - participants experiencing severe toxicities should receive additional care and/or switch to an alternative therapy
  - participants whose disease progresses should switch to a second-line intervention
- **Such changes to intervention**
  - **are consistent with the trial protocol (even if not written down)**
  - **do not cause bias, and**
  - **should not be considered to be deviations from intended intervention**





# Trial authors may not fully specify when changes to initial intervention should occur

- e.g. a cancer trial protocol may not define progression, or specify the second-line drug that should be used in patients who progress
- e.g. for “usual care” comparator, a protocol may not specify the interventions consistent with usual care
- It may be necessary for RoB 2 users to **document changes to intervention that they do and do not consider to be consistent with the trial protocol**, or describe interventions that are consistent with usual care



# The role of blinding

## Blinding of participants and trial personnel should prevent:

- contamination (application of one of the interventions in participants intended to receive the other)
- switches to non-protocol interventions
- non-adherence by trial participants



# The role of blinding

## Blinding of participants and trial personnel:

- **not appropriate** in pragmatic trials whose goal is to compare interventions in individuals who are aware of their care
- **essential** in trials that aim to eliminate placebo effects and isolate specific effects of protocol interventions

Blinding of outcome assessors is considered separately in RoB 2 (see domain 4)



# The effect of interest



# What is the effect of interest?

## Investigators conducted a large randomized trial of screening for colorectal cancer:

- Patients registered with family doctors were individually randomised to receive an invitation to attend for screening
- 55% of patients in the intervention arm attended screening
- All patients were followed up for colorectal cancer 10 years after randomization, using routine data

**What can we learn from this trial? Who would be interested in the results?**



JAMA | **Original Investigation**

# Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality

## The CAP Randomized Clinical Trial

Richard M. Martin, PhD; Jenny L. Donovan, PhD; Emma L. Turner, PhD; Chris Metcalfe, PhD; Grace J. Young, MSc; Eleanor I. Walsh, MSc; J. Athene Lane, PhD; Sian Noble, PhD; Steven E. Oliver, PhD; Simon Evans, MD; Jonathan A. C. Sterne, PhD; Peter Holding, MSc; Yoav Ben-Shlomo, PhD; Peter Brindle, MD; Naomi J. Williams, PhD; Elizabeth M. Hill, MSc; Siaw Yein Ng, PhD; Jessica Toole, MSc; Marta K. Tazewell, MSc; Laura J. Hughes, BA; Charlotte F. Davies, PhD; Joanna C. Thorn, PhD; Elizabeth Down, MSc; George Davey Smith, DSc; David E. Neal, MD; Freddie C. Hamdy, MD; for the CAP Trial Group

**IMPORTANCE** Prostate cancer screening remains controversial because potential mortality or quality-of-life benefits may be outweighed by harms from overdetection and overtreatment.


**OBJECTIVE** To evaluate the effect of a single prostate-specific antigen (PSA) screening intervention and standardized diagnostic pathway on prostate cancer–specific mortality.

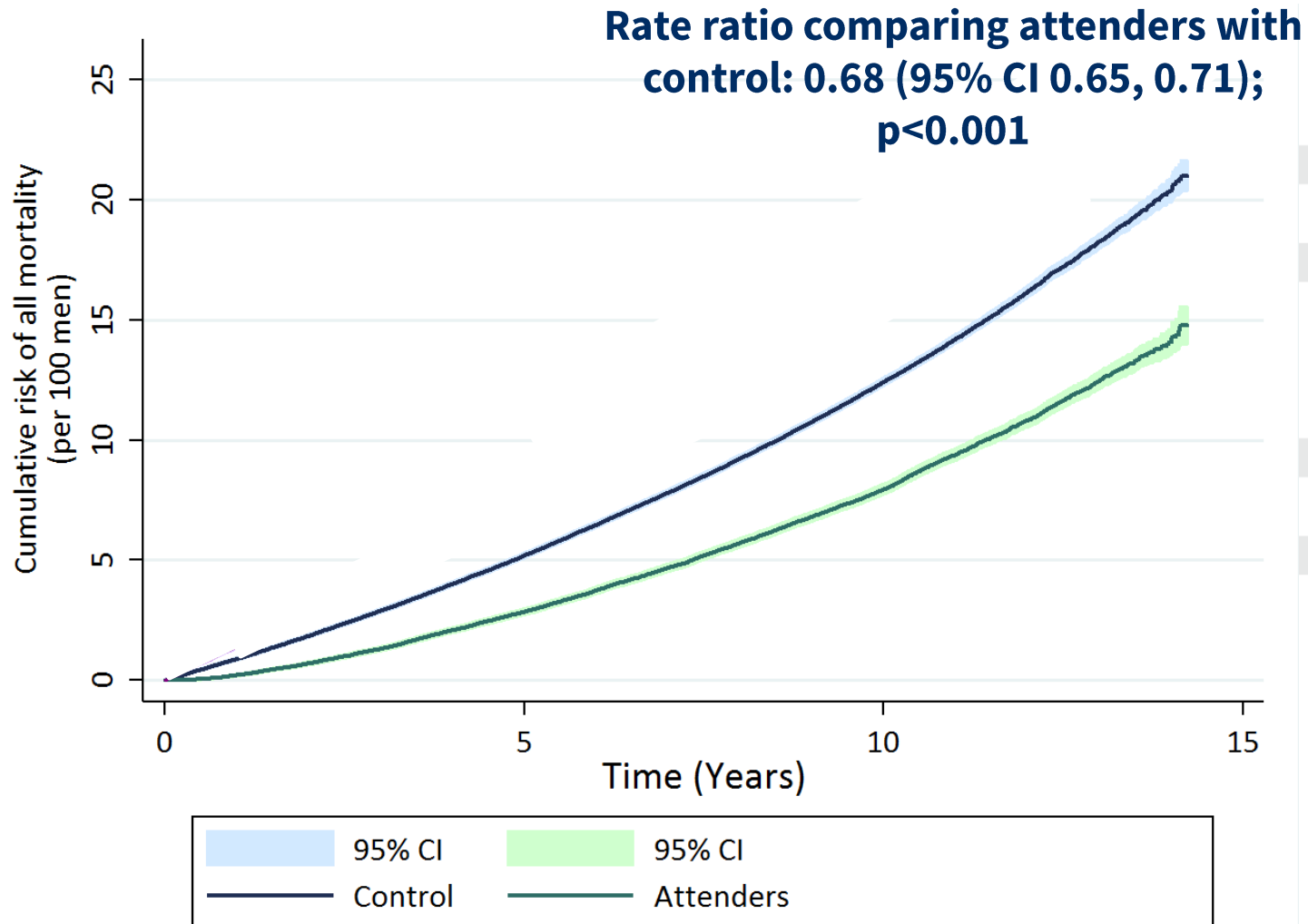
**DESIGN, SETTING, AND PARTICIPANTS** The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) included 419 582 men aged 50 to 69 years and was conducted at 573 primary care practices across the United Kingdom. Randomization and recruitment of the practices occurred between 2001 and 2009; patient follow-up ended on March 31, 2016.

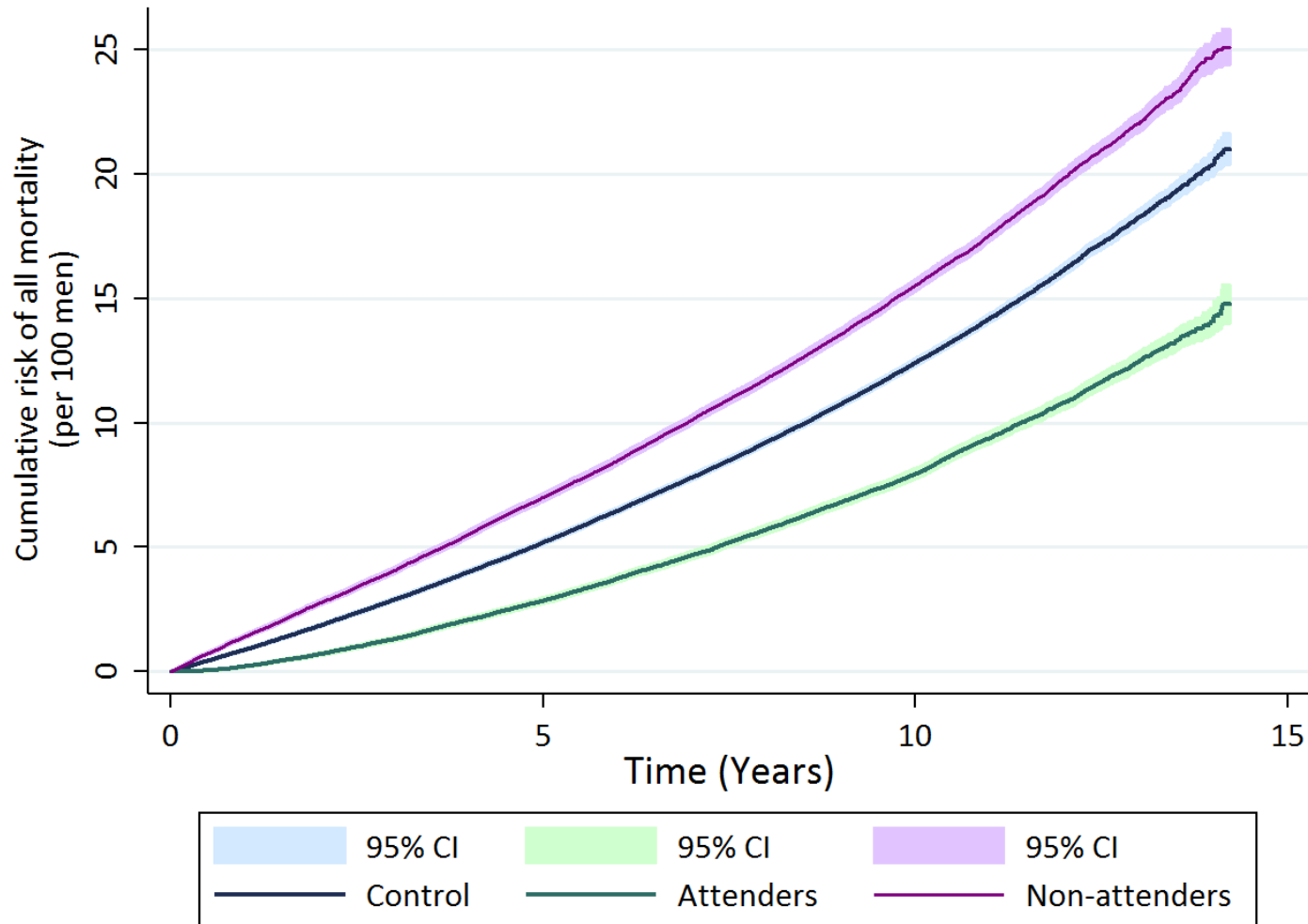
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 [Related article page 896](#)

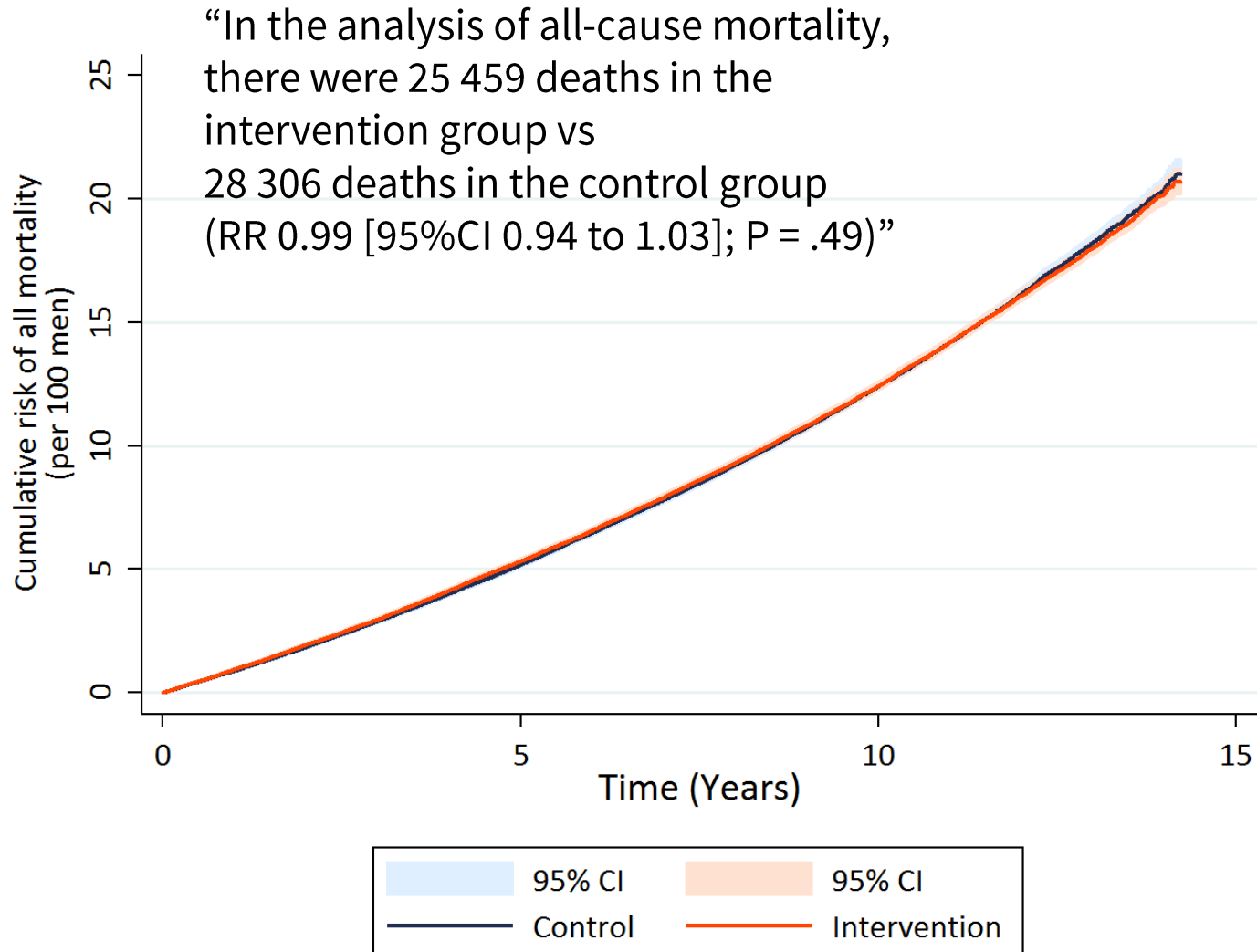
 [Supplemental content](#)

 [CME Quiz at   
 \[jamanetwork.com/learning\]\(https://jamanetwork.com/learning\)   
 and CME Questions page 929](#)









**We could be interested in either or both of:**

- **the effect of assignment to intervention**
  - of most interest to a policymaker considering whether to introduce a screening programme
  - the ‘intention-to-treat’ (ITT) effect
  
- **the effect of adhering to intervention**
  - of most interest to a patient deciding whether to be screened
  - the ‘per-protocol’ effect

Questions?



# Risk of bias in the effect of assignment to intervention



# Estimating the effect of assignment to intervention

## Cochrane Reviews usually assess the effect of assignment to intervention (the ITT effect)

- we should use an ‘intention-to-treat’ (ITT) analysis:
  - analyse participants in the intervention groups to which they were randomized, regardless of the intervention received
  - include all randomized participants in the analysis
  - measure outcome data on all participants



# Which result to select?

**When the effect of interest is that of assignment to intervention, the trial result should be chosen according to the following order of preference:**

1. The result corresponding to a full ITT analysis
2. The result corresponding to an analysis that adheres to ITT principles except that participants with missing outcome data are excluded
  - This is sometimes described as a ‘modified intention-to-treat’ (mITT) analysis)
  - Such an analysis **does not** prevent bias due to missing outcome data: this is addressed in the corresponding domain
3. A result corresponding to an ‘as treated’ or naïve ‘per-protocol’ analysis, or an analysis from which eligible trial participants were excluded

# The role of blinding in the risk of bias assessment

## Providing that the analysis is appropriate:

- In **blinded trials**, risk of bias due to deviations from intended intervention **will be low**
- In **unblinded trials**, risk of bias due to deviations from intended intervention **will usually be low**
  - This is because the effect of assignment to intervention depends on the **net effect** of:
    - the effect of the interventions specified in the trial protocol; and
    - the degree and type of adherence to these interventions

# Bias due to deviations from intended intervention

**For the effect of assignment to intervention, we assess only deviations that arose because of the trial context:**

- whether the process of **recruiting and engaging with participants** affected their behaviour
  - e.g. participants assigned to the comparator group may feel unlucky and therefore seek the experimental intervention
- whether **trial personnel undermined trial comparisons** by implementing non-protocol interventions or failing to implement the protocol interventions
  - unconscious processes (e.g. lack of equipoise leading to administration of non-protocol interventions in one group)
  - conscious processes (e.g. arising from a conflict of interest)



# When is there a high risk of bias

**Deviations arising because of the trial context will be a problem only if**

- they affect the outcome
- they are unbalanced between intervention groups



# Signalling questions

## Effect of assignment to intervention

**2.1. Were participants aware of their assigned intervention during the trial?**

**2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?**

**2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?**

**2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome?**

**2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?**

**2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?**

**2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?**

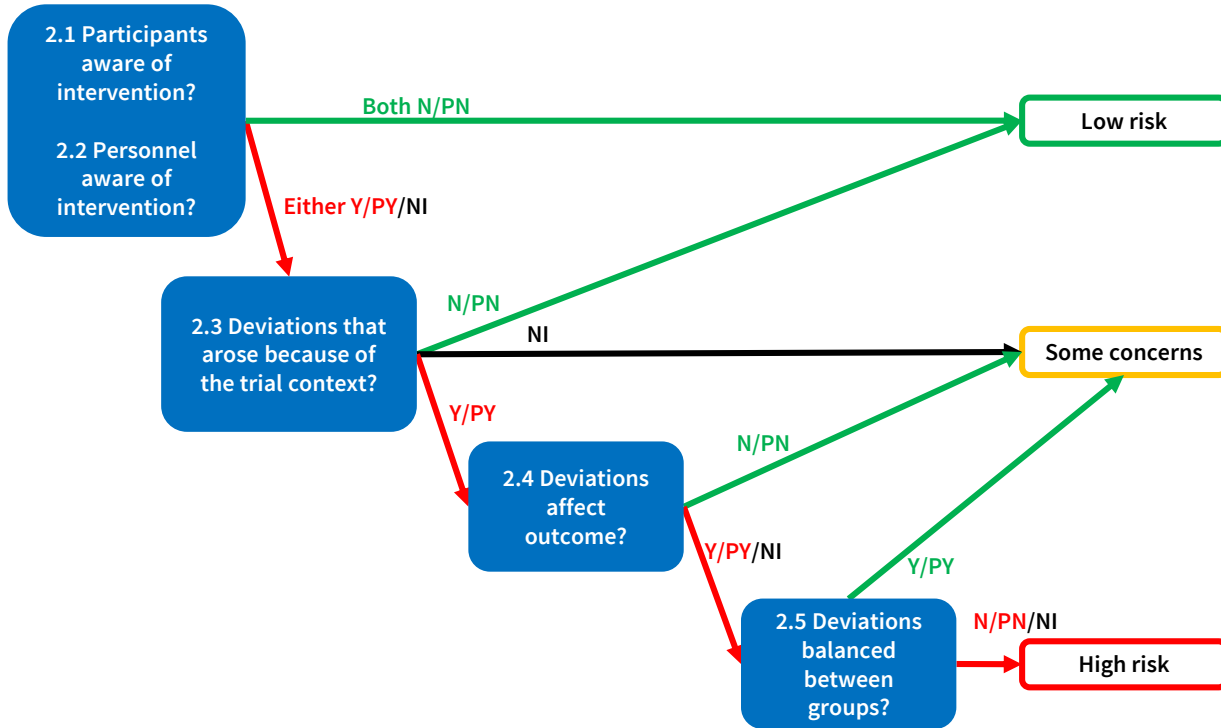
**Blinding**

**Deviations**

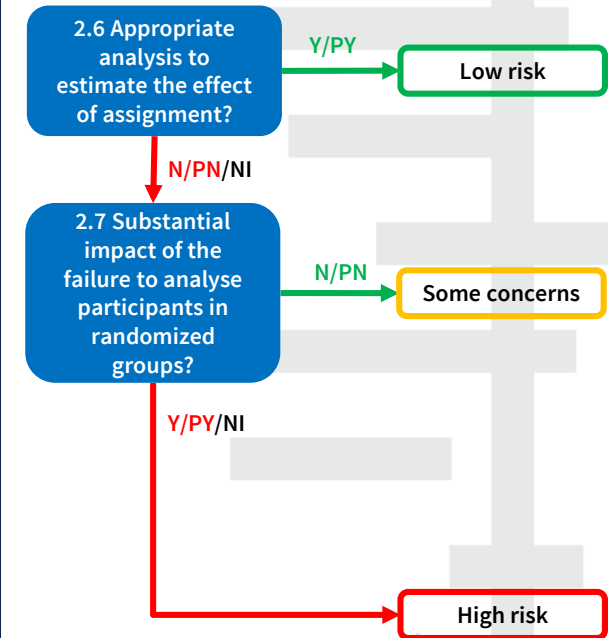
**Appropriate  
analysis**

## Effect of assignment to intervention

### Part 1: Questions 2.1 to 2.5



### Part 2: Questions 2.6 & 2.7



### Criteria for the domain



# Discussion



# Risk of bias in the effect of adhering to intervention



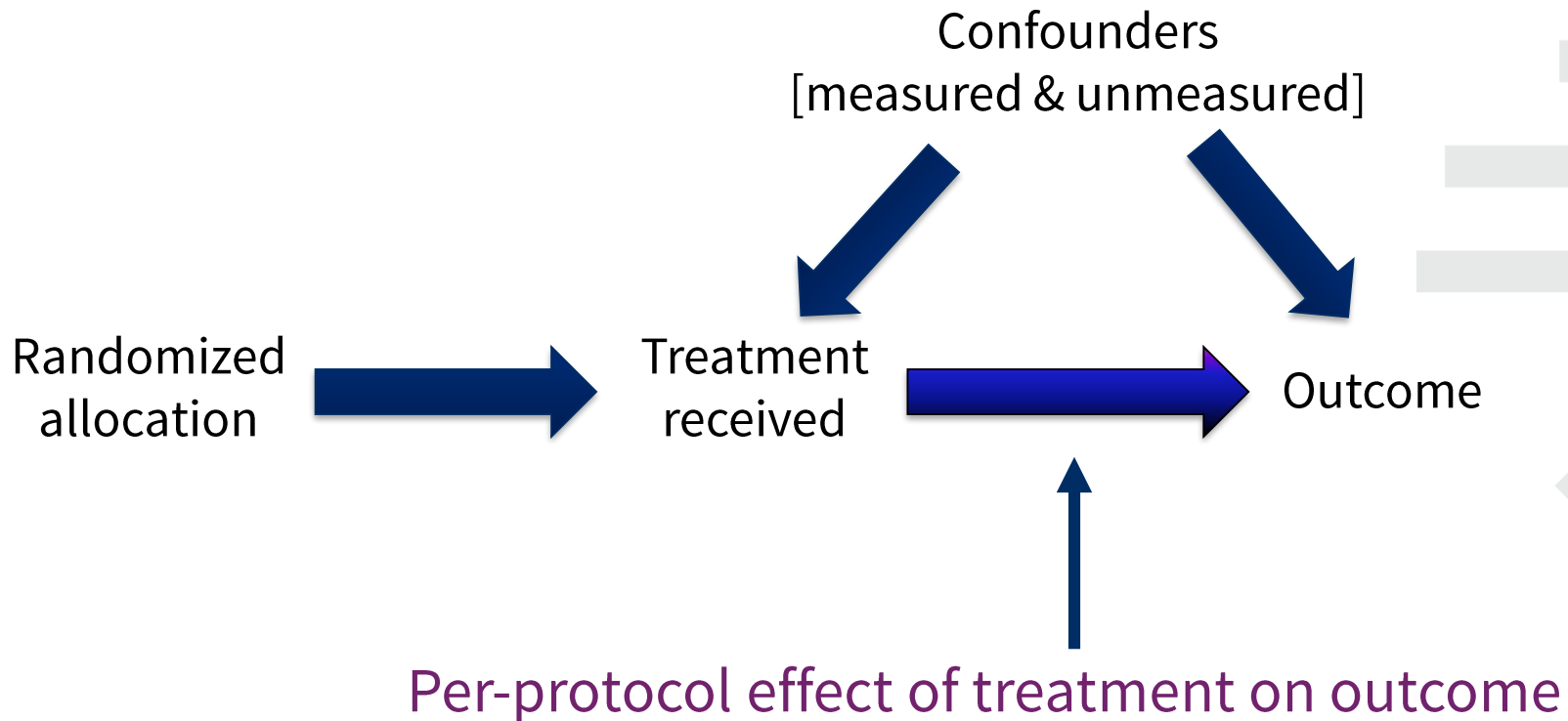
# Estimating the effect of adhering to intervention

**Two commonly used approaches to analysis may be seriously biased:**

- naïve ‘per protocol’ analyses restricted to individuals in each group who started and adhered to the interventions
- ‘as-treated’ analyses: participants analysed according to the intervention received, even if their randomized allocation was to a different treatment group

**There are methods that can sometimes be used...**

# Randomization as an instrumental variable (IV)



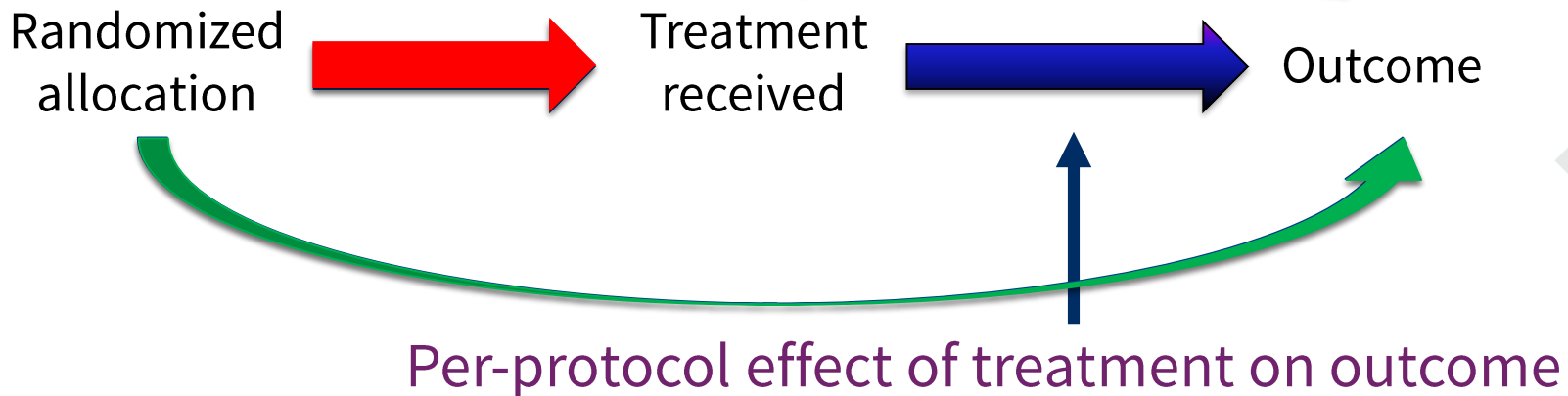
# Using an IV analysis to estimate the per-protocol effect

There is no confounding of the associations of:

(a) Randomized allocation and treatment received

(b) Randomized allocation and the outcome

An IV analysis exploits these associations to estimate the per-protocol effect





*The NEW ENGLAND JOURNAL of MEDICINE*

STATISTICS IN MEDICINE

## Per-Protocol Analyses of Pragmatic Trials

Miguel A. Hernán, M.D., Dr.P.H., and James M. Robins, M.D.

Pragmatic trials are designed to address real-world questions about options for care and thereby guide decisions by patients, clinicians, and other stakeholders. Pragmatic trials are often analyzed according to the intention-to-treat principle, which requires that patients assigned to a treatment strategy are kept in that group during the analysis, even if they deviated from their assigned treatment strategy after randomization.<sup>1-3</sup> The result of an intention-to-treat analysis is affected by the trial-specific pattern of adherence to the treatment strategies under study and therefore may not be directly relevant for guiding decisions in clinical settings with different adherence patterns. In fact,

it and the other half did not. In the second trial, all the patients assigned to the active treatment received it. In neither study did any patient assigned to standard of care receive active treatment. An intention-to-treat analysis may show a treatment effect in the first trial but not in the second. This could occur even if the biologic effect of active treatment were identical in the two studies. Furthermore, in a head-to-head trial of two active treatments that have differential adherence because of a mild, easily palliated side effect, an intention-to-treat analysis may misleadingly indicate a beneficial effect of the less efficacious treatment.

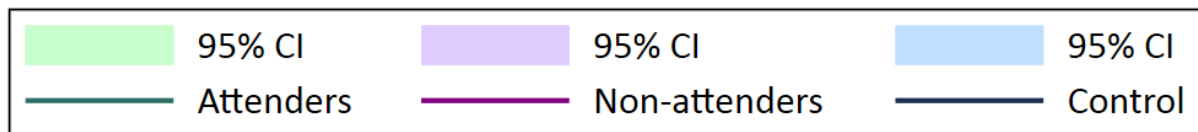
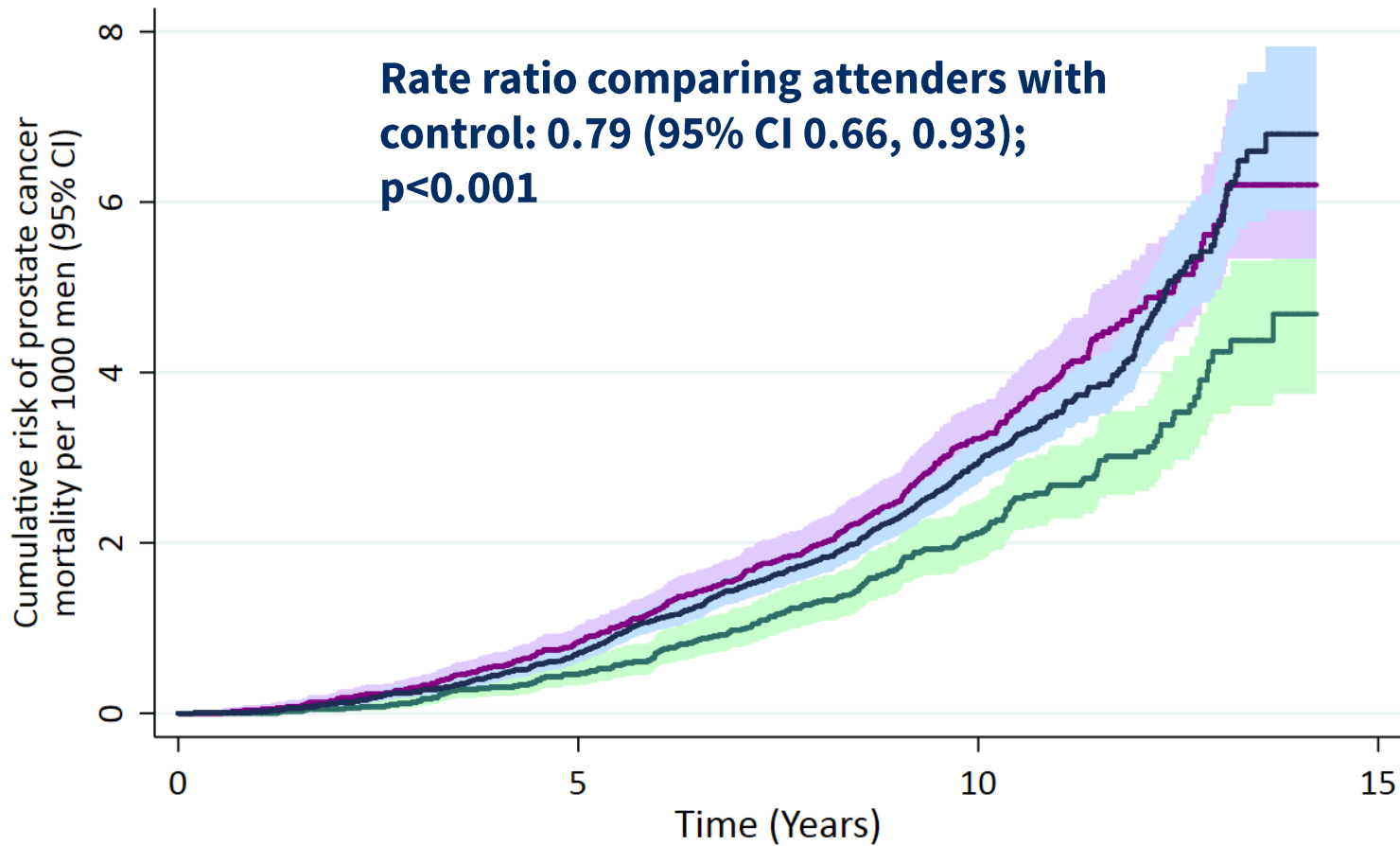
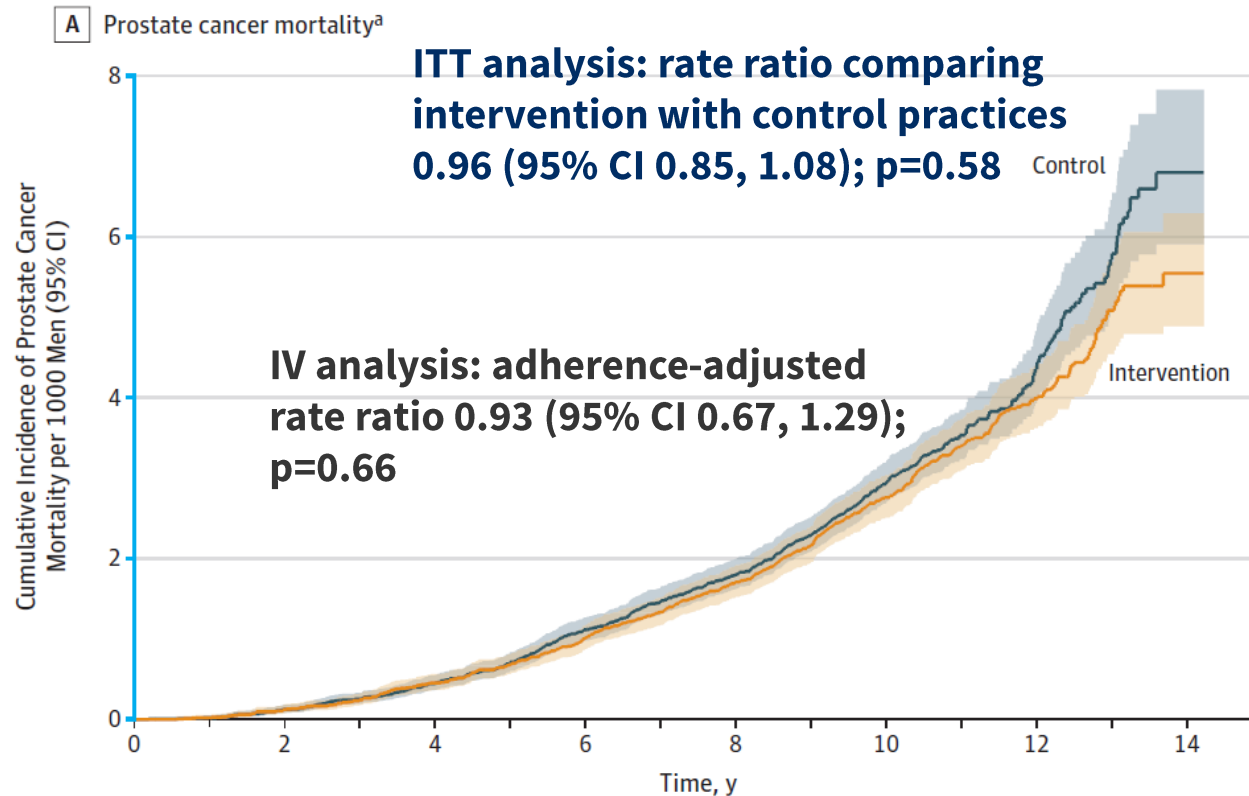


Figure 2. Cumulative Incidence of Prostate Cancer Detection and Mortality in the Single Prostate-Specific Antigen Testing Intervention Group vs Standard Practice (Control)



No. at risk									
Intervention	189 386	184 370	178 777	172 702	165 313	95 089	38 003	16 49	
Control	219 439	213 705	207 112	199 382	190 408	107 186	23 811	18 16	
No. of events									
Intervention		23	60	98	118	136	81	33	0
Control		27	68	135	134	170	75	38	0

# Bias due to deviations from intended intervention

- Deviations from intended intervention **may lead to bias in the effect of adhering to intervention**
- We therefore have different signalling questions for the effect of adhering to intervention
- RoB 2 users should identify in advance which types of deviation they are concerned about



**Is the review team's aim for this result...?**

- to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- occurrence of non-protocol interventions
- failures in implementing the intervention that could have affected the outcome
- non-adherence to their assigned intervention by trial participants

<b>Experimental</b>	Steroid	<b>Comparator</b>	Control	<input type="checkbox"/> Tri
<b>Specify which outcome</b>	Mortality	<b>Specify the numerical result</b>		<input type="checkbox"/> Sta
<b>Is the review team's aim for this result to assess...?</b>	adhering to intervention (the 'per-protocol' effect)	<b>Weight for analysis</b>	1	<input checked="" type="checkbox"/> No
<b>If the aim is to assess the effect of adhering to intervention...(select one at least)</b>	<input type="checkbox"/> occurrence of non-protocol interventions <input type="checkbox"/> failures in implementing the intervention that could have affected the outcome <input checked="" type="checkbox"/> non-adherence to their assigned intervention by trial participants			<input type="checkbox"/> Co
<b>Domain 1</b>	<b>Domain 2</b>	<b>Domain 3</b>	<b>Domain 4</b>	<b>Domain 5</b>
<b>Overall bias</b>				
<b>Deviations from intended interventions</b>				
<b>Signalling questions</b>				<b>Response</b>
2.1 Were participants aware of their assigned intervention during the trial?				Y
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?				Y

# Bias due to deviations from intended interventions

## Effect of adhering to intervention

2.1. Were participants aware of their assigned intervention during the trial?

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?

2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?

2.7. If N/PN/NI to 2.3, Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?

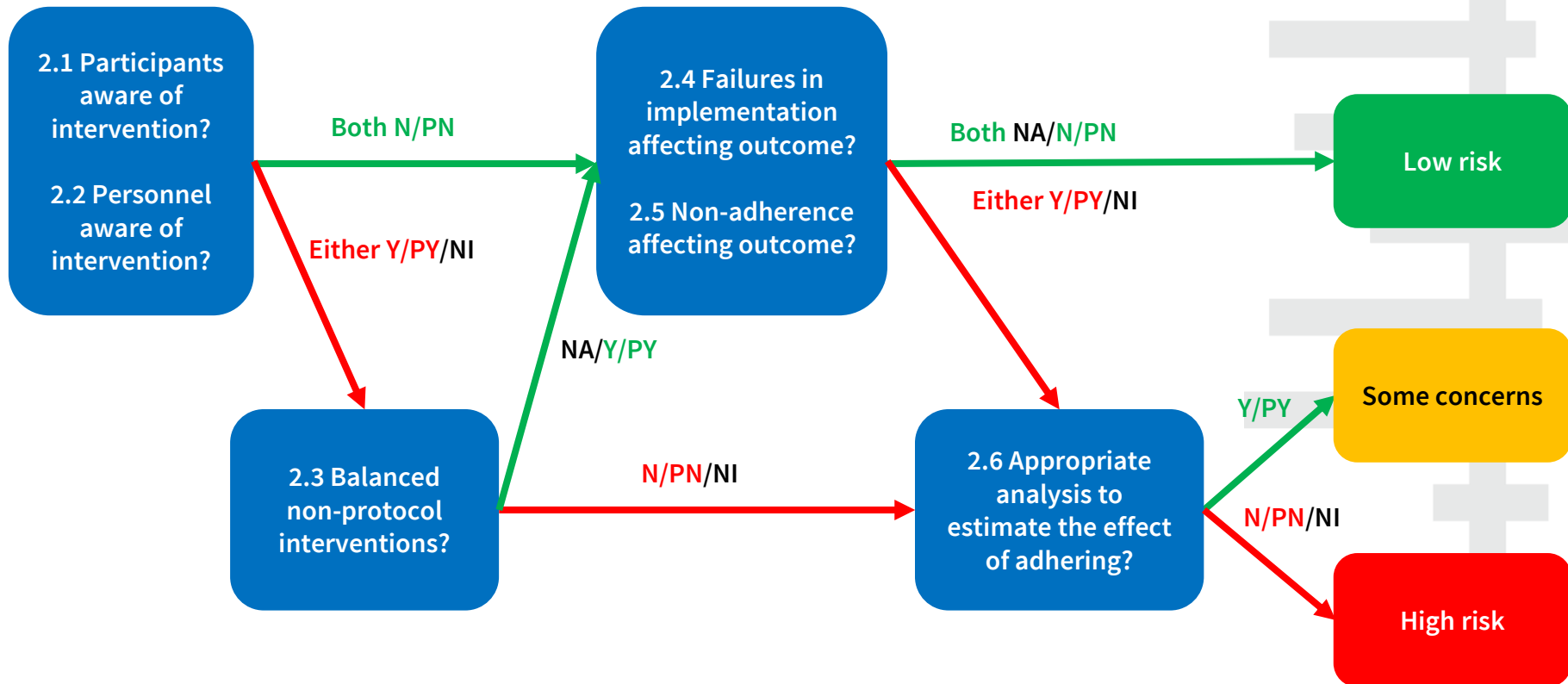
Blinding

Specific  
deviations

Overcome  
by analysis?

# Bias due to deviations from intended interventions

Effect of adhering to intervention



# Questions

